

Appendix A. Steering Committee Members

Appendix B. Sample of Randomized Controlled Trials

The following are citations for the RCTs that were assessed using the Cochrane Risk of Bias tool. The 30 RCTs that were used to examine reliability of consensus assessments by individual reviewers are marked with an asterisk (*). Overall 154 RCTs were included in the final sample. We assessed 161 RCTs but replaced 7 of these as they did not evaluate therapeutic interventions (Beedie et al., Boardman et al., D'Souza et al., Dyke et al., Kamlin et al., Pierce et al., Umemura et al.).

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Appendix C. Guidelines for Risk of Bias Assessments

This table was taken from the Cochrane Handbook of Reviews of Effectiveness of Interventions (Table 8.5.c (modified): Criteria for judging risk of bias in the 'Risk of bias' assessment tool).¹⁰ The last column was added to provide decision rules specific to this project.

SEQUENCE GENERATION Was the allocation sequence adequately generated? (Short form: <i>Adequate sequence generation?</i>)		
<p>Criteria for a judgement of 'YES' (i.e. low risk of bias).</p>	<p>The investigators describe a random component in the sequence generation process such as:</p> <ul style="list-style-type: none"> • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. <p>*Minimization may be implemented without a random element, and this is considered to be equivalent to being random.</p>	<p>The investigators describe the use of stratification or permuted blocking (use of computer implied).</p>
<p>Criteria for the judgement of 'NO' (i.e. high risk of bias).</p>	<p>The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:</p> <ul style="list-style-type: none"> • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. <p>Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example:</p> <ul style="list-style-type: none"> • Allocation by judgement of the 	

	<p>clinician;</p> <ul style="list-style-type: none"> • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention. 	
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.	Description only includes 'random', 'randomly generated', 'randomized', etc.

ALLOCATION CONCEALMENT

Was allocation adequately concealed? (Short form: *Allocation concealment?*)

Criteria for a judgement of 'YES' (i.e. low risk of bias).	<p>Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:</p> <ul style="list-style-type: none"> • Central allocation (including telephone, web-based and pharmacy-controlled randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes. 	
Criteria for the judgement of 'NO' (i.e. high risk of bias).	<p>Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:</p> <ul style="list-style-type: none"> • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); • Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure. 	
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	<p>Insufficient information to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.</p>	

BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS

Was knowledge of the allocated interventions adequately prevented during the study? (Short form: *Blinding?*)

****Assess this domain based on the pre-determined primary outcome****

Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: <ul style="list-style-type: none"> No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias. 	Investigators describe the use of a <u>matched</u> placebo or discuss how placebos were similar in some way (e.g., appearance, taste, etc.)
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: <ul style="list-style-type: none"> No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias. 	
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: <ul style="list-style-type: none"> Insufficient information to permit judgement of 'Yes' or 'No'; The study did not address this outcome. 	Study is only described as 'double-blind' or 'placebo-controlled'.

INCOMPLETE OUTCOME DATA

Were incomplete outcome data adequately addressed? (Short form: *Incomplete outcome data addressed?*)

Criteria for a judgement of 'YES' (i.e. low risk of bias).	<p>Any one of the following:</p> <ul style="list-style-type: none"> No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods. 	<p>Any one of the following:</p> <ul style="list-style-type: none"> ≥90%* of enrolled patients are included in the analysis AND withdrawals and reasons for withdrawals are balanced between groups and appear unrelated to outcome; A true intention-to-treat analysis was conducted. <p>*90% is used as a guideline.</p>
Criteria for the judgement of 'NO' (i.e. high risk of bias).	<p>Any one of the following:</p> <ul style="list-style-type: none"> Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the 	<p>Any one of the following:</p> <ul style="list-style-type: none"> <90%* of enrolled patients are included in the analysis; Substantial proportion of patients withdrew from the study, even if they are included in an ITT analysis. <p>*90% is used as a guideline.</p>

	<p>intervention received from that assigned at randomization;</p> <ul style="list-style-type: none"> Potentially inappropriate application of simple imputation. 	
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	<p>Any one of the following:</p> <ul style="list-style-type: none"> Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided); The study did not address this outcome. 	

SELECTIVE OUTCOME REPORTING		
Are reports of the study free of suggestion of selective outcome reporting? (Short form: <i>Free of selective reporting?</i>)		
Assess this domain based on ALL study outcomes		
Criteria for a judgement of 'YES' (i.e. low risk of bias).	<p>Any of the following:</p> <ul style="list-style-type: none"> The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon). 	Outcomes described in the Methods section are reported on in the Results section.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	<p>Any one of the following:</p> <ul style="list-style-type: none"> Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest 	

	<p>in the review are reported incompletely so that they cannot be entered in a meta-analysis;</p> <ul style="list-style-type: none"> • The study report fails to include results for a key outcome that would be expected to have been reported for such a study. 	
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.	

OTHER POTENTIAL THREATS TO VALIDITY		
<p>Was the study apparently free of other problems that could put it at a risk of bias? (Short form: <i>Free of other bias?</i>)</p> <p><i>**Assess this domain based on: design-specific risks of bias; early stopping for benefit; severe baseline imbalances; inappropriate influence of funders** (a full list and other potential biases are provided in Section 8.14.1.6 of the Cochrane Handbook). Record any other potential sources that you feel may compromise the internal validity of a given study.</i></p>		
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The study appears to be free of other sources of bias.	<p>With respect to "inappropriate influence of study sponsors", any one of the following:</p> <ul style="list-style-type: none"> • The study received no funding; • The study was only funded by non-industry (e.g., government); • The study declares the source of funding and the role of the sponsor (i.e., specifies that sponsor was removed from the conduct of the study).
Criteria for the judgement of 'NO' (i.e. high risk of bias).	<p>There is at least one important risk of bias. For example, the study:</p> <ul style="list-style-type: none"> • Had a potential source of bias related to the specific study design used; or • Stopped early due to some data-dependent process (including a formal-stopping rule); or • Had extreme baseline imbalance; or • Has been claimed to have been fraudulent; or • Had some other problem. 	<p>With respect to "inappropriate influence of study sponsors", any one of the following:</p> <ul style="list-style-type: none"> • One or more of the authors are industry employees or are receiving speaking grants; • The sponsor is directly involved in the conduct of the trial.
Criteria for the judgement of	There may be a risk of bias, but there is	With respect to "inappropriate influence of

<p>'UNCLEAR' (uncertain risk of bias).</p>	<p>either:</p> <ul style="list-style-type: none"> • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias. 	<p>study sponsors”, any one of the following:</p> <ul style="list-style-type: none"> • There is no mention of the funding source; • Industry funding is declared with no description of role in the study.
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Appendix D. Variables for Data Extraction from Randomized Controlled Trials

VALIDITY OF RISK OF BIAS: DATA EXTRACTION GUIDE		
Field	Response	Comments
<i>Publication characteristics</i>		
Please enter the following publication characteristics: RefID Publication title: Publication year: Citation: Full journal title: First author: Country of corresponding author: Number of authors: Was there a working group? Type of journal: Impact factor: RefID PubTitle PubDate Citation Journal LeadAuthor GeoLocation NumAuthors	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> General medical journal <input type="checkbox"/> Specialty medical journal	
<i>Trial characteristics</i>		
What is the study design?	<input type="checkbox"/> RCT parallel <input type="checkbox"/> RCT crossover <input type="checkbox"/> RCT factorial <input type="checkbox"/> RCT split body	RCT parallel: A trial that compares two groups of people concurrently, one of which receives the intervention of interest and one of which is a control group . Some parallel trials have more than two comparison groups and some compare different

		<p>interventions without including a non-intervention control group. (Also called independent group design.)</p> <p>RCT crossover: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, the participants are randomly allocated to receive them in either the order A, B or the order B, A. Particularly appropriate for study of treatment options for relatively stable health problems. The time during which the first intervention is taken is known as the first period, with the second intervention being taken during the second period.</p>
Based on the study hypothesis/objectives, which study type is described by the authors?	<input type="checkbox"/> Efficacy/Superiority <input type="checkbox"/> Equivalence <input type="checkbox"/> Non-inferiority <input type="checkbox"/> Not declared <input type="checkbox"/> None of the above <input type="checkbox"/> Unclear	<p>Efficacy/Superiority: A study in which the authors intended to demonstrate a statistically significant difference between treatments.</p> <p>Equivalence: A study in which the authors intended to show that there was no statistically significant difference between treatments.</p> <p>Non-inferiority: A study in which the authors intended to show that the new treatment effect is not worse than the standard treatment effect.</p>
In your opinion, what study type is consistent with the methods described?	<input type="checkbox"/> Efficacy/Superiority <input type="checkbox"/> Equivalence <input type="checkbox"/> Non-inferiority <input type="checkbox"/> None of the above <input type="checkbox"/> Unclear	I.e., in your opinion, is the study type consistent with what the authors have classified it as?
What is the unit of randomization?	<input type="checkbox"/> Individual <input type="checkbox"/> Cluster	Cluster RCTs could include randomization of classrooms or schools, practices or hospitals, etc.
What is the nature of the intervention?	<input type="checkbox"/> Behavioral/Psychological <input type="checkbox"/> Device <input type="checkbox"/> Drug <input type="checkbox"/> Natural health product <input type="checkbox"/> Surgical <input type="checkbox"/> Vaccine <input type="checkbox"/> Other	<p>Natural health products include:</p> <ul style="list-style-type: none"> -Vitamins and minerals -Herbal remedies -Homeopathic medicines -Traditional medicines such as traditional Chinese medicines -Probiotics, and -Other products like amino acids and essential fatty acids. <p>(http://www.hc-sc.gc.ca/dhp-mps/prodnatur/index-</p>

		<p>eng.php)</p> <p>A device is “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:</p> <ul style="list-style-type: none"> -recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, -intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or -intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of it's primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes." <p>(http://www.fda.gov/CDRH/DEVADVICE/312.html)</p>
What is the intervention type?	<input type="checkbox"/> Pharmacological <input type="checkbox"/> Nonpharmacological	<p>Pharmacological includes drugs, natural health products, vaccines</p> <p>Non-pharmacological includes behavioural/educational, devices, surgical</p>
Was the treatment mode a:	<input type="checkbox"/> Flexible dose <input type="checkbox"/> Fixed dose <input type="checkbox"/> Unclear <input type="checkbox"/> N/A	
What intervention(s) are tested?		Specify the intervention(s) evaluated in the trial
Is the study placebo controlled?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear	
How many arms does the study have?		
Is the study multicenter?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear	
If yes, how many study sites are involved?		
Is the study multinational?	<input type="checkbox"/> One country <input type="checkbox"/> Multinational	
What is the enrolled sample size?		
Is a sample size calculation reported?	<input type="checkbox"/> Yes	

	<input type="checkbox"/> No	
What is the primary/secondary diagnostic category involved in the study?	<input type="checkbox"/> Acute Respiratory Infections <input type="checkbox"/> Airways <input type="checkbox"/> Anaesthesia <input type="checkbox"/> Back <input type="checkbox"/> Bone, Joint and Muscle Trauma <input type="checkbox"/> Breast Cancer <input type="checkbox"/> Colorectal Cancer <input type="checkbox"/> Consumers and Communication <input type="checkbox"/> Cystic Fibrosis and Genetic Disorders <input type="checkbox"/> Dementia and Cognitive Improvement <input type="checkbox"/> Depression, Anxiety and Neurosis <input type="checkbox"/> Developmental, Psychosocial and Learning Problems <input type="checkbox"/> Drugs and Alcohol <input type="checkbox"/> Ear, Nose and Throat Disorders <input type="checkbox"/> Effective Practice and Organisation of Care <input type="checkbox"/> Epilepsy <input type="checkbox"/> Eyes and Vision <input type="checkbox"/> Fertility Regulation <input type="checkbox"/> Gynaecological Cancer <input type="checkbox"/> HIV/AIDS <input type="checkbox"/> Haematological Malignancies <input type="checkbox"/> Heart <input type="checkbox"/> Hepato-Biliary <input type="checkbox"/> Hypertension <input type="checkbox"/> Incontinence <input type="checkbox"/> Infectious Diseases <input type="checkbox"/> Inflammatory Bowel Disease and Functional Bowel Disorders <input type="checkbox"/> Injuries <input type="checkbox"/> Lung Cancer <input type="checkbox"/> Menstrual Disorders and Subfertility <input type="checkbox"/> Metabolic and Endocrine Disorders <input type="checkbox"/> Movement Disorders <input type="checkbox"/> Multiple Sclerosis	

	<input type="checkbox"/> Musculoskeletal <input type="checkbox"/> Neuromuscular Disease <input type="checkbox"/> Occupational Safety and Health <input type="checkbox"/> Oral Health <input type="checkbox"/> Pain, Palliative and Supportive Care <input type="checkbox"/> Peripheral Vascular Diseases <input type="checkbox"/> Pregnancy and Childbirth <input type="checkbox"/> Prostatic Diseases and Urologic Cancers <input type="checkbox"/> Public Health <input type="checkbox"/> Renal <input type="checkbox"/> Schizophrenia <input type="checkbox"/> Sexually Transmitted Diseases <input type="checkbox"/> Skin <input type="checkbox"/> Stroke <input type="checkbox"/> Tobacco Addiction <input type="checkbox"/> Upper Gastrointestinal and Pancreatic Diseases <input type="checkbox"/> Wounds <input type="checkbox"/> Other	
Specify condition being treated:		
What was the treatment duration?		
What is the funding source?	<input type="checkbox"/> Industry <input type="checkbox"/> Government <input type="checkbox"/> Academic <input type="checkbox"/> Foundation <input type="checkbox"/> No funding <input type="checkbox"/> Other <input type="checkbox"/> Not declared	
Specify source of funding:		
<i>Outcomes and conclusions</i>		
Primary outcome:		
Is the primary outcome:	<input type="checkbox"/> Objective <input type="checkbox"/> Subjective	<p>Objective outcomes include all cause mortality, measures based on a recognized laboratory procedure, surgical or instrumental outcomes and other objective measures.</p> <p>Subjective outcomes include patient reported outcomes, physician assessed disease outcomes, measures combined from several outcomes, and withdrawals or</p>

		study dropouts. (Wood <i>et al.</i> BMJ 2008;336:601-605.)
Source of outcome assessment:	<input type="checkbox"/> Administrative data <input type="checkbox"/> Automated data <input type="checkbox"/> Clinician's assessment <input type="checkbox"/> Laboratory measure <input type="checkbox"/> Self-report <input type="checkbox"/> Other	
What is the effect estimate of the primary outcome?		

Appendix E. Meta-Analyses and Cohort Studies used for NOS Assessments

EPC Systematic Reviews:

Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, Trikalinos T, Lau J. *Breastfeeding and maternal and infant health outcomes in developed countries*. Evidence Report/Technology Assessment No. 153 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center, under Contract No. 290-02-0022). AHRQ Publication No. 07-E007. Rockville, MD: Agency for Healthcare Research and Quality. April 2007.

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37. Yekta Z, Ayatollah H, Porali R, Farzin A. The effect of pre-pregnancy body mass index and gestational weight gain on pregnancy outcomes in urban care settings in Irma-Iran. *BMC Pregnancy Childbirth* 2006;6:15.
38. Yogev Y, Langer O, Xenakis E, Rosenn B. The association between glucose challenge test, obesity and pregnancy outcome in 6390 non-diabetic women. *J Matern Fetal Neonatal Med* 2005;17:29-34.

Appendix F. Decision Rules for Application of the Newcastle-Ottawa Scale

The following coding instructions are taken from the Newcastle-Ottawa Scale website, available here: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Text in italics indicates additional guidance for reviewers agreed upon during the initial training teleconference.

CODING MANUAL FOR COHORT STUDIES

SELECTION

1) Representativeness of the exposed cohort

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample of women from some general population. For example, subjects derived from groups likely to contain middle class, better educated, health oriented women are likely to be representative of postmenopausal estrogen users while they are not representative of all women (e.g. members of a health maintenance organisation (HMO) will be a representative sample of estrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant users of estrogen).

- a) truly representative of the average in the community*
- b) somewhat representative of the average in the community*
- c) selected group of users e.g. nurses, volunteers
- d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

- a) drawn from the same community as the exposed cohort*
- b) drawn from a different source*
- c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

- a) secure record (e.g. surgical records, *medical records*)*
- b) structured interview*
- c) written self report

4) Demonstration that outcome of interest was not present at start of study

In the case of mortality studies, outcome of interest is still the presence of a disease/incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

- a) yes*
- b) no

COMPARABILITY

1) Comparability of cohorts on the basis of the design or analysis

A maximum of 2 stars can be allotted in this category

Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)

Please see the accompanying background sheet to determine what confounders are considered important for each review topic.

If the outcome/condition of interest is gender-specific (i.e. depression in pregnancy), only evaluate 'a' on whether or not the researchers controlled for age.

- a) study controls for age/sex (the most important factor)*
- b) study controls for any additional factor*

OUTCOME

1) Assessment of outcome

For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to x-rays would be required.

- a) independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.)*
- b) record linkage (e.g. identified through ICD codes on database records)*
- c) self-report (i.e. no reference to original medical records or x-rays to confirm the outcome)
- d) no description.

2) Was follow-up long enough for outcomes to occur

Please see the accompanying background sheet to determine what the minimum required follow-up period is for each review topic.

- a) yes*
- b) no

If the follow-up period is reported with a mean and a range, and the mean is longer than the required minimum, rate it as 'yes.'

3) Adequacy of follow-up of cohorts

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.

- a) complete follow-up, all subjects accounted for*
- b) subjects lost to follow-up are unlikely to introduce bias – small number lost <20%
- c) follow-up rate <80% and no description of those lost
- d) no description *or unclear*

If follow-up rates vary by outcome, use the outcome included in the meta-analysis of the systematic review the article is included in.

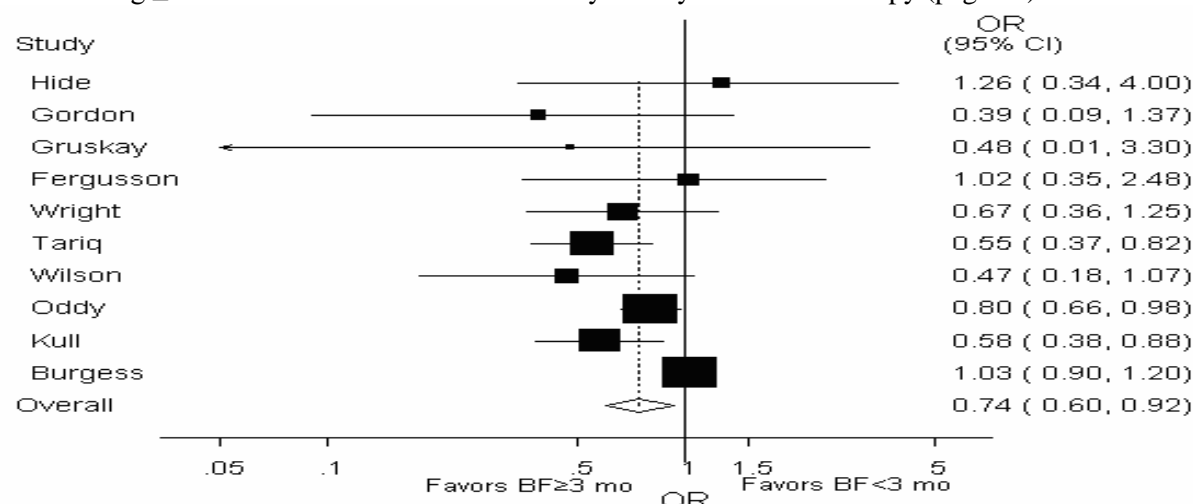
If <20% of subjects were lost to follow-up, but the difference between groups is large consider downgrading to 'c,' especially if no reasons for difference in follow-up are provided.

Appendix G. Supplementary Information for NOS Assessments

Additional background information provided to study participants to assist in making quality assessments. Information was based on the initial systematic reviews, or where necessary, expert opinion.

Breastfeeding and Maternal and Infant Health Outcomes in Developed Countries (AHRQ Report Number 153)

Source: Figure 9. Meta-analysis of prospective cohort studies of the association between asthma risk and breastfeeding ≥ 3 months for children without family history of asthma or atopy (page 46)



Key Question: What are the benefits and harms for infants and children in terms of short-term outcomes, such as infectious diseases (including otitis media, diarrhea, and lower respiratory tract infections), sudden infant death syndrome and infant mortality, and longer-term outcomes such as cognitive development, childhood cancer (including leukemia), type 1 and 2 diabetes, asthma, atopic dermatitis, cardiovascular disease (including hypertension), hyperlipidemia, and obesity, compared among those who mostly breastfeed, mostly formula feed, and mixed feed; and how are these outcomes associated with duration of the type of feeding? Do the harms and benefits differ for any specific subpopulations based on socio-demographic factors?

Primary Outcome:

-risk of developing asthma

Population:

-healthy term infants in developed countries; preterm infants in developed countries (for NEC and cognitive development); healthy mothers in developed countries

Comparability:

-maternal age
-socioeconomic status, parental smoking, [family history of atopy]

Followup:

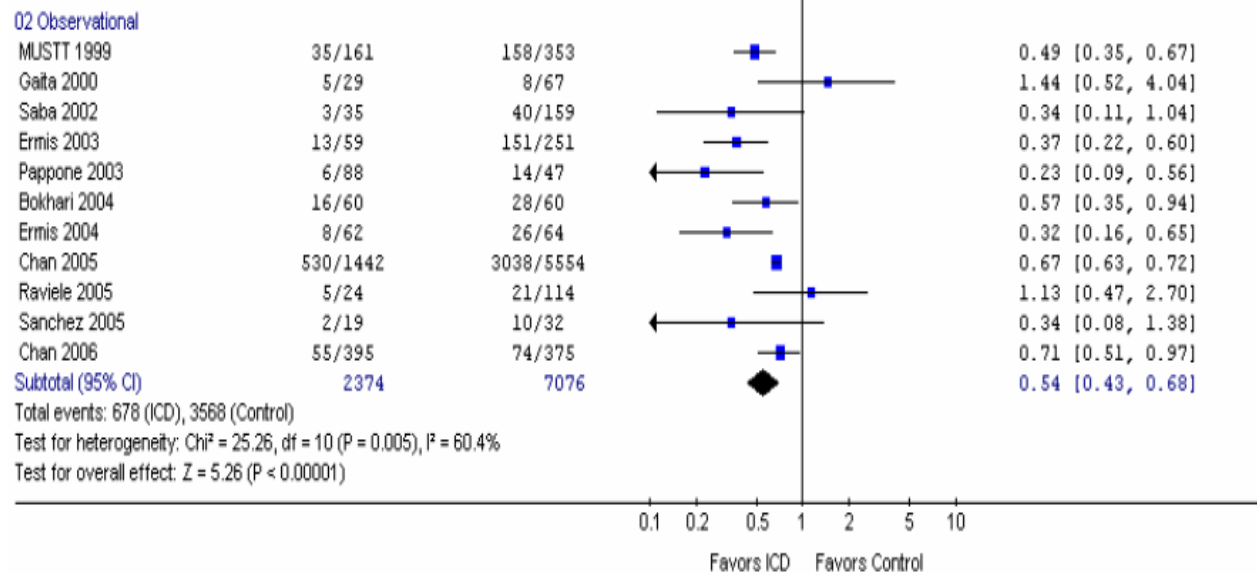
-minimum duration of followup: 5 years (60 months)

Adequacy of followup:

$\geq 80\%$ considered adequate

Cardiac Resynchronization Therapy and Implantable Cardiac Defibrillators in Left Ventricular Systolic Dysfunction (AHRQ Report Number 152)

Source: Figure 15. Metagraph of all-cause mortality: ICD alone (page 157) [only 9 of 11 studies]



Key Question: In adult patients with symptomatic or asymptomatic left ventricular (LV) systolic dysfunction, what is the efficacy and effectiveness of cardiac resynchronization therapy (CRT) alone, implantable cardiac defibrillators (ICD) alone, or combined CRT-ICD devices compared to usual medical therapy? What is the efficacy and effectiveness of single-chamber ICD compared to that of dual-chamber ICD? How safe is CRT alone, ICD alone, or combined CRT-ICD devices? Which patients would benefit from ICD alone, CRT alone, or combined CRT-ICD devices?

Primary Outcome:

-all cause mortality

Population:

-patients with asymptomatic LV systolic dysfunction or symptomatic heart failure (HF) and left ventricular ejection fraction (LVEF) $\leq 35\%$
 -since the implantation procedure can only be performed in specialized centers, review authors determined that all facilities were representative of patients in usual practice

Comparability:

-NYHA class
 -age, sex, race, etiology of heart failure (e.g., ischemic), LVEF, QRS width, rhythm (normal sinus rhythm, atrial fibrillation), medication use

Followup:

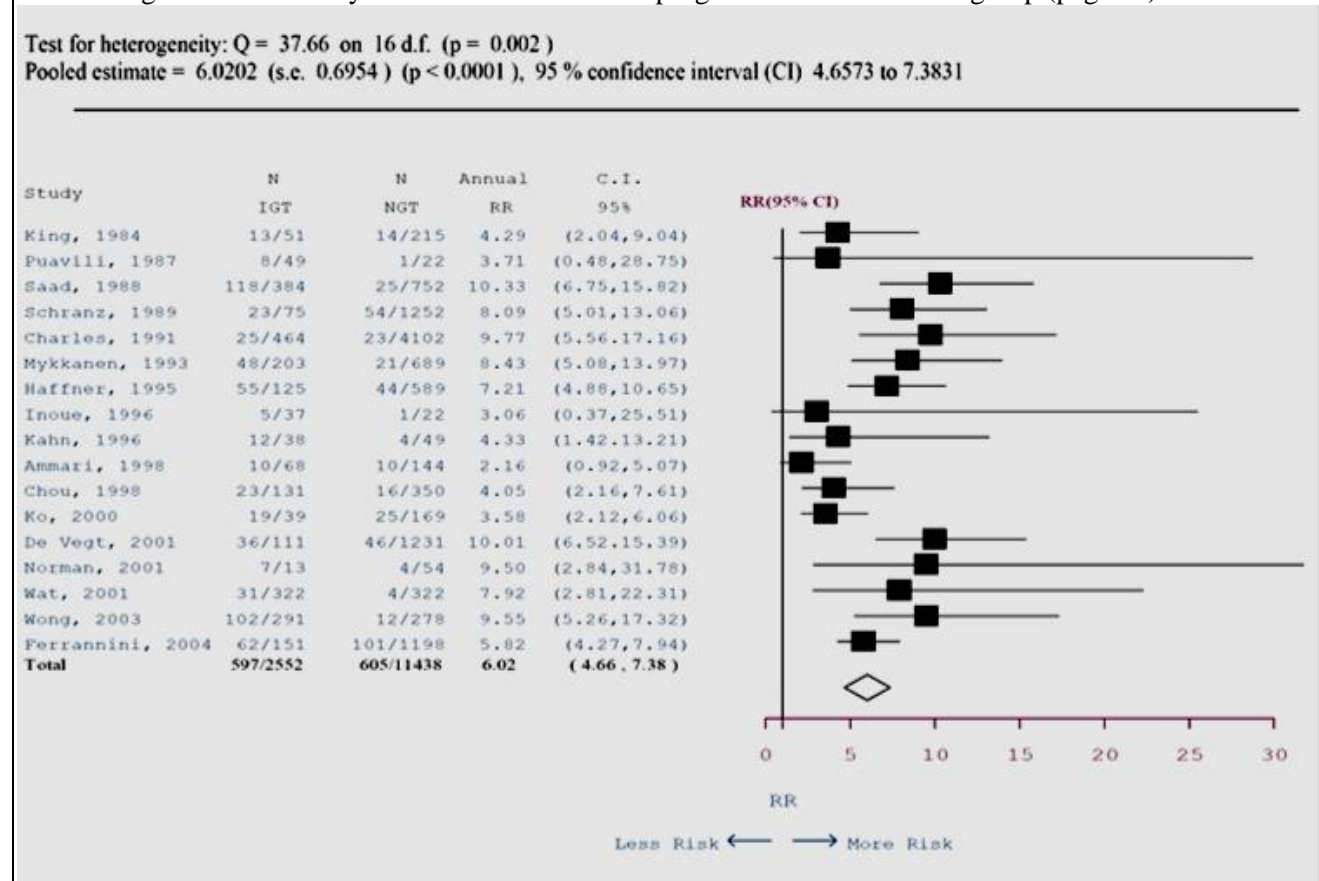
-minimum duration of followup: 1 year (12 months)

Adequacy of followup:

$\geq 80\%$ considered adequate

Diagnosis, Prognosis, and Treatment of Impaired Glucose Tolerance and Impaired Fasting Glucose (AHRQ Report Number 128)

Source: Figure 6. Meta-analysis of annualized RR for progression to DM in IGT group (page 47)



Key Question: What is the relationship between IFG and IGT? For those individuals identified with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), what are the short- and long-term risks for developing negative health outcomes? Does this risk vary by subpopulation, such as sex, race, obesity, age, or other such risk factors as blood pressure or elevated lipid levels?

Primary Outcome:

-progression from IFG or IGT to diabetes mellitus

Population:

-pt with IFG or IGT (cutoff criteria varies)

Comparability:

- age, sex
- blood pressure, elevated lipid levels

Followup:

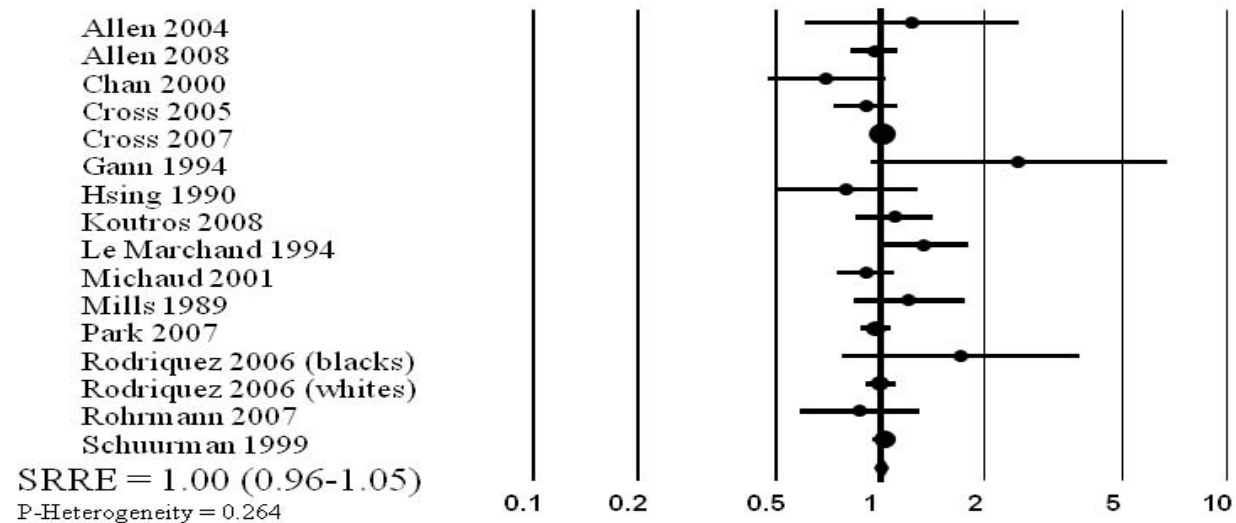
-minimum duration of followup: 3 years (36 months)

Adequacy of followup:

->=80% considered adequate

A Review and Meta-analysis of Prospective Studies of Red and Processed Meat Intake and Prostate Cancer (Alexander, Mink, Cushing, Scurman. Nutrition Journal 2010;0:50)

Source: Figure 1. Meta-analysis of prospective studies of red meat intake and prostate cancer (page 12)
Author & Year **RR and 95% CI**



Objective/Aim: To estimate the summary associations between red or processed meat intake and prostate cancer; evaluate associations among men with advanced disease; estimate dose-response trends; evaluate potential sources of heterogeneity; assess the potential for publication bias?

Primary outcome:

-occurrence of prostate cancer

Participants:

-men only

Comparability:

-age, race
-energy intake, smoking, family history of cancer

Followup:

-minimum duration of followup: 5 years (60 months)

Adequacy of followup:

≥80% considered adequate

A Meta-analysis of Depression During Pregnancy and the Risk of Preterm Birth, Low Birth Weight and Intrauterine Growth Restriction (Grote, Bridge, Gavin, Melville, Iyengar and Katon. Arch Gen Psychiatry 2010;67(10):1012-24)

Source: Table 2. Effect of antenatal depression on outcomes of PTB, LBW, and IUGR (p. 1016). (exclude Suri and Wisner—Case Series)

Table 2. Effect of Antenatal Depression on Outcomes of PTB, LBW, and IUGR

Outcome	No. of Studies	Relative Risk (95% CI) ^a	P Value	Heterogeneity		
				Q _{df} Within	P Value	Variance Explained, %
PTB	20	1.13 (1.06-1.21)	<.001	49.0 ₁₉	<.001	61
LBW	11	1.18 (1.07-1.30)	.001	33.8 ₁₀	<.001	70
IUGR	12	1.03 (0.99-1.08)	.14	22.4 ₁₁	.02	51

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; LBW, low birth weight; PTB, preterm birth.

^a Pooled effect size was estimated using the random-effects model.

Objectives/Aims: To estimate the risk of preterm birth (PTB), low birth weight (LBW), and intrauterine growth restriction (IUGR) associated with antenatal depression

Primary outcome:

-preterm birth (PTB was defined as birth prior to 37 weeks' gestation)

Participants:

-pregnant women only

Comparability:

-maternal age
-smoking/substance abuse, race/ethnicity or SES, previous pre-term birth, SSRI antidepressant use, educational level, marital status

Followup:

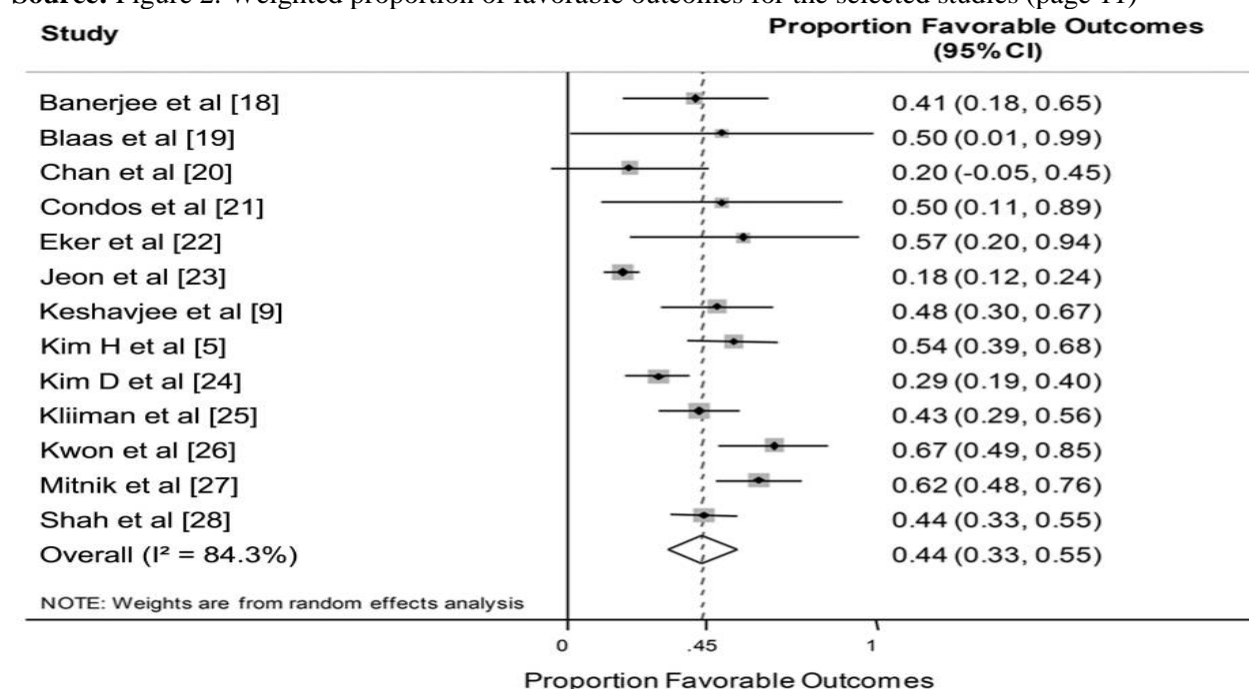
-Not applicable (outcomes [preterm birth/birth weight] are obtained as soon as birth occurs)

Adequacy of followup:

->80% considered adequate

Treatment Outcomes among Patients with Extensively Drug-Resistant Tuberculosis: Systematic Review and Meta-Analysis (Jacobson, Tierney, Jeon, Mitnick and Murray. Clinical Infectious Diseases 2010;51(1):6-14)

Source: Figure 2. Weighted proportion of favorable outcomes for the selected studies (page 11)



Objective/Aim: To assess extensively drug-resistant (XDR) tuberculosis treatment outcomes and to identify therapeutic approaches associated with favorable outcomes

Primary outcome:

-number of patients with favorable outcomes [Favorable outcomes as defined by WHO—Cure: treatment completion plus at least 5 consecutive negative cultures during the last year of treatment; Treatment completion: treatment completion but <5 cultures performed in the last year of treatment]

Participants:

-confirmed XDR TB by drug susceptibility testing of *M. tuberculosis* cultures

Comparability:

-age
-HIV prevalence among patients with XDR TB receiving treatment; sex; number of drugs in treatment regimens; number of “likely active drugs” in a treatment regimen; percentage of patients who received a later-generation fluoroquinolone; percentage of patients who received linezolid; percentage of patients who underwent surgery

Followup:

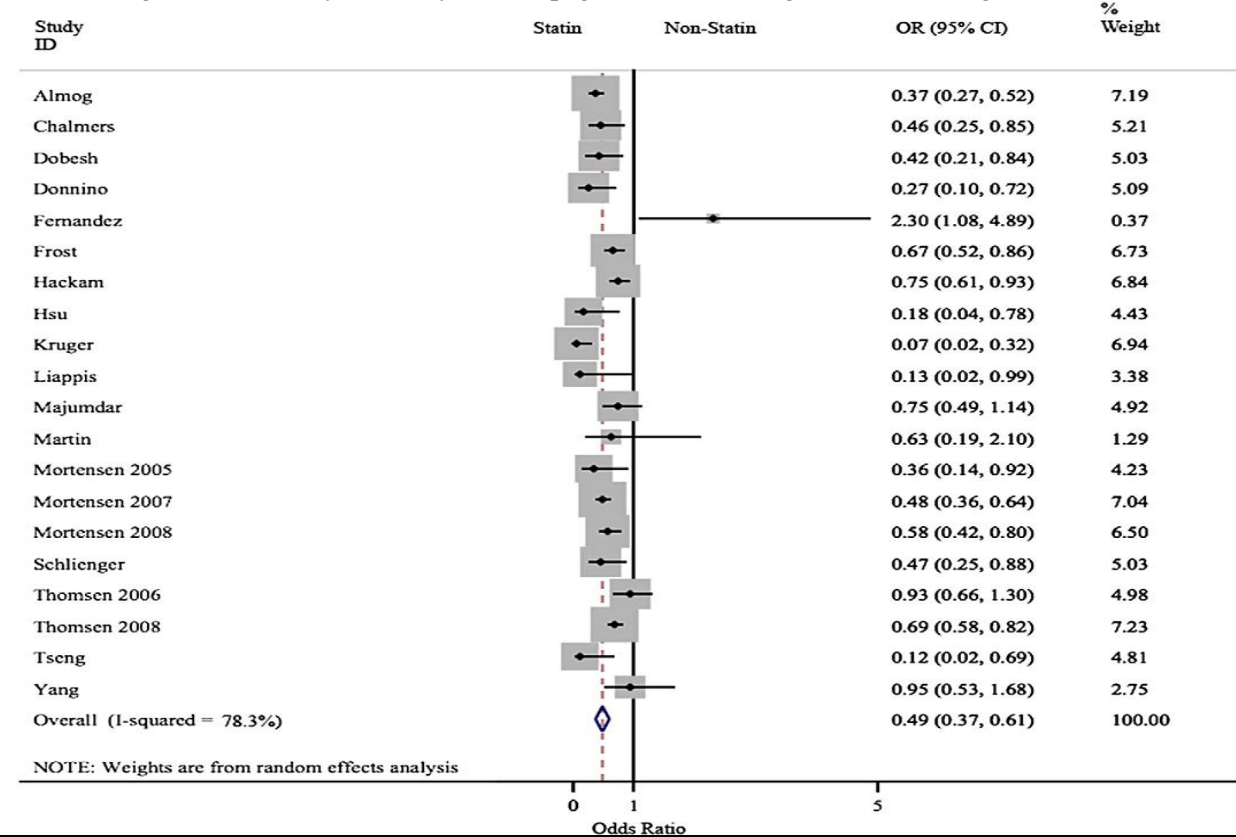
-minimum duration of followup: 1 year (12 months)

Adequacy of followup:

≥80% considered adequate

The effect of statins on mortality from severe infections and sepsis: A systematic review and meta-analysis (Janda, Young, FitzGerald, Etminan, Swiston. Journal of Critical Care 2010;25:656e7—656e22)

Source: Figure 2. Mortality from any cause. (page e15) (excluding Frost and Tseng—RCTs)



Objective/Aim: The aim of this study was to systematically review the literature on the effect of statins on mortality in patients with infection and/or sepsis

Primary outcome:

-mortality (all cause)

Participants:

-both adult and pediatric patients
-included sepsis or various infections: bacteremia, pneumonia, HIV, hepatitis B, C, and A, and cytomegalovirus

Comparability:

-age
-sex, severity of disease, co-morbidities, history of illness, medication use

Followup:

-minimum duration of followup: 30 days

Adequacy of followup:

≥80% considered adequate

Overweight and Obesity in Mothers and Risk of Preterm Birth and Low Birth Weight Infants: Systematic Review and Meta-Analyses (McDonald, Han, Mulla, and Beyene. BMJ 2010;341:c3428).

Source: Figure 2. Forest plot of risk of preterm birth before 37 weeks in overweight and obese women compared with women of normal weight in cohort studies (page 7)

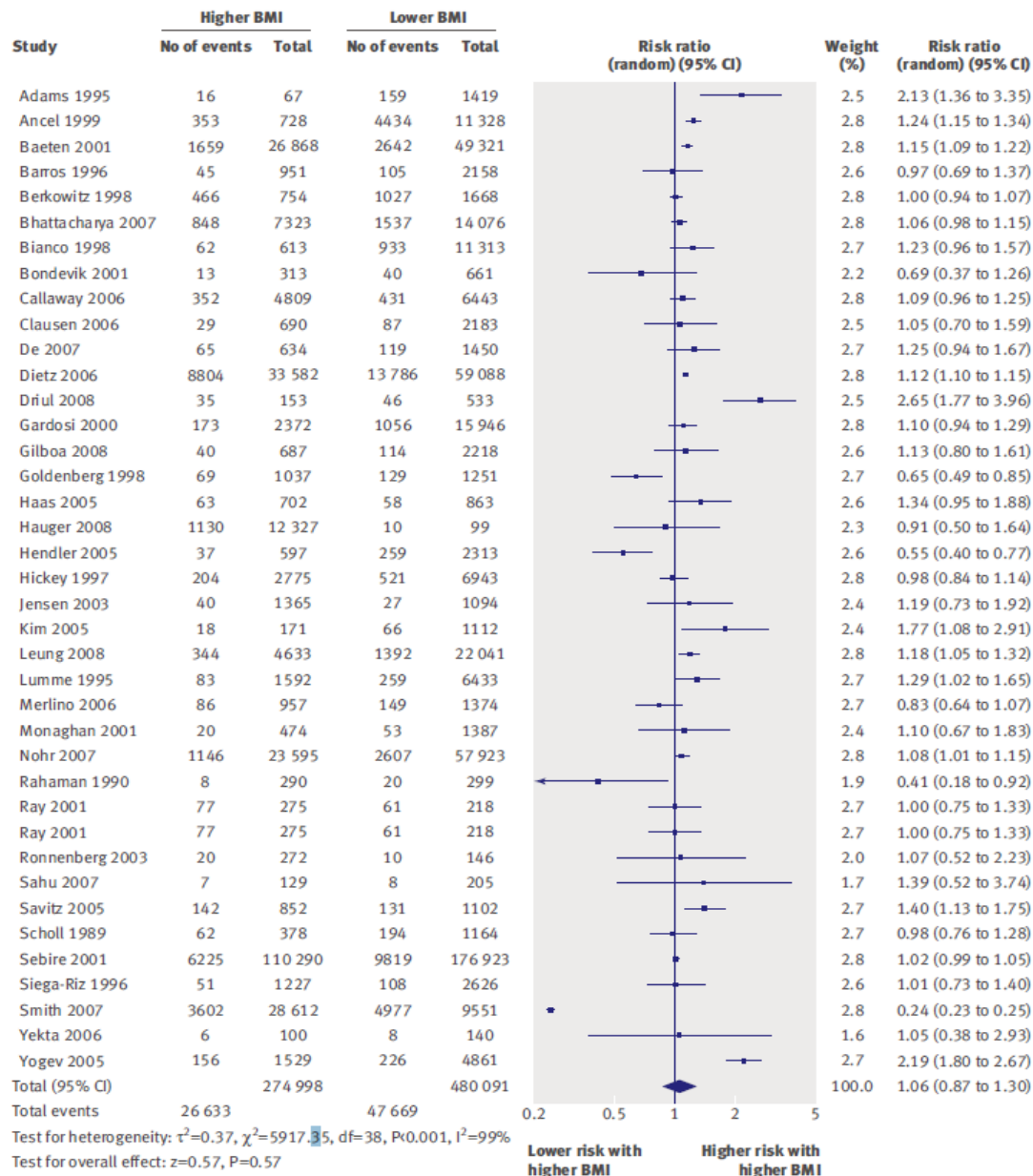


Fig 2 | Forest plot of risk of preterm birth before 37 weeks in overweight and obese women compared with women of normal weight in cohort studies. BMI=body mass index

Objectives/Aims: To determine the relation between overweight and obesity in mothers and preterm birth and low birth weight in singleton pregnancies in developed and developing countries.

Primary outcome:

-preterm birth (<37 weeks gestation)

Participants:

-pregnant women with singleton pregnancies only

Comparability:

-age
-race, parity, smoking, marital status, education, socio-economic status, co-morbidities (e.g., diabetes, pre-eclampsia, gestational diabetes)

Followup:

-Not applicable (outcomes [preterm birth/birth weight] are obtained as soon as birth occurs)

Adequacy of followup:

-≥80% considered adequate

Appendix H. Description of Randomized Controlled Trials

Publication characteristics (N=154)

Variable	n (%)	Overall risk of bias assessment		
		High	Unclear	Low
Number of authors (mean, SD)	6.8 (3.3)			
Working group				
Yes	14 (9.1)	11	3	0
No	139 (90.9)	61	78	1
Type of journal				
General medical journal	19 (12.3)	10	9	0
Specialty medical journal	135 (87.7)	62	72	1
Country of corresponding author				
Australia	7 (4.6)	5	2	0
Austria	1 (0.7)	1	0	0
Belgium	1 (0.7)	0	1	0
Canada	3 (2.0)	2	1	0
Chile	1 (0.7)	0	1	0
China	6 (3.9)	3	3	0
Denmark	2 (1.3)	1	1	0
Egypt	1 (0.7)	0	1	0
Finland	1 (0.7)	1	0	0
France	4 (2.6)	0	4	0
Germany	6 (3.9)	2	4	0
Greece	4 (2.6)	0	4	0
India	1 (0.7)	0	1	0
Iran	2 (1.3)	0	2	0
Italy	13 (8.4)	3	10	0
Japan	5 (3.3)	2	3	0
Mexico	1 (0.7)	0	1	0
the Netherlands	6 (3.9)	3	3	0
New Zealand	1 (0.7)	0	1	0
Norway	3 (2.0)	1	2	0
Poland	1 (0.7)	0	1	0
Scotland	1 (0.7)	0	1	0
Singapore	3 (2.0)	1	2	0
South Africa	2 (1.3)	2	0	0
South Korea	2 (1.3)	0	2	0
Spain	2 (1.3)	1	1	0
Sweden	5 (3.2)	3	2	0
Taiwan	2 (1.3)	0	2	0
Turkey	5 (3.3)	1	4	0
United Kingdom	13 (8.4)	7	6	0
U.S.	49 (31.8)	33	15	1
Impact factor (mean, SD)	5.0 (7.6)			

SD = standard deviation

Trial characteristics (N=154)

Variable	n (%)	Overall risk of bias assessment		
		High	Unclear	Low
Study design				
RCT crossover	21 (13.6)	10	11	0
RCT factorial	3 (2.0)	2	1	0
RCT parallel	126 (81.8)	59	66	1
RCT split body	4 (2.6)	1	3	0
Study type				
Efficacy/Superiority	130 (84.4)	61	69	0
Equivalence	9 (5.8)	4	4	1
Non-inferiority	2 (1.3)	2	0	0
None of the above	6 (3.9)	1	5	0
Unclear	7 (4.5)	4	3	0
Unit of randomization				
Cluster	7 (4.6)	5	2	0
Individual	147 (95.5)	67	79	1
Nature of intervention				
Behavioral/Psychological	17 (11.0)	9	8	0
Device	10 (6.5)	3	7	0
Drug	82 (53.3)	42	39	1
Natural health product	6 (3.9)	1	5	0
Surgical	18 (11.7)	7	11	0
Vaccine	1 (0.7)	1	0	0
Other	20 (13.0)	9	11	0
Intervention type				
Nonpharmacological	67 (43.5)	29	38	0
Pharmacological	87 (56.5)	43	43	1
Dosing				
Fixed dose	79 (51.3)	38	40	1
Flexible dose	31 (20.1)	13	18	0
Not applicable	41 (26.6)	21	20	0
Unclear	3 (2.0)	0	3	0
Placebo controlled				
Yes	55 (35.7)	27	27	1
No	97 (63.0)	45	52	0
Unclear	2 (1.3)	0	2	0
Number of arms (median, range)	2 (2-7)			
Multicenter				
Yes	40 (26.0)	25	14	1
No	100 (64.9)	40	60	0
Unclear	14 (9.1)	7	7	0
Number of centers (range)	1-327			
Multinational				
Yes	7 (4.6)	5	2	0
No	147 (95.5)	67	79	1
Sample size (median, IQR)	63 (39-123)			
Sample size calculation reported				
Yes	80 (51.9)	40	39	1
No	74 (48.1)	32	42	0
Funding source (all that apply)				
Academic	18 (11.7)	6	12	0
Foundation	26 (16.9)	11	15	0
Government	40 (26.0)	22	18	0
Industry	42 (27.3)	33	9	0
No funding	7 (4.6)	3	3	1
Not declared	47 (30.5)	13	34	0
Other	8 (5.2)	2	6	0

Primary Diagnostic Category	n (%)
Acute Respiratory Infections	1 (0.7)
Airways	6 (3.9)
Anesthesia	5 (3.2)
Back	1 (0.7)
Bone, Joint and Muscle Trauma	4 (2.6)
Breast Cancer	2 (1.3)
Colorectal Cancer	5 (3.3)
Cystic Fibrosis and Genetic Disorders	1 (0.7)
Depression, Anxiety and Neurosis	6 (3.9)
Drugs and Alcohol	3 (2.0)
Ear, Nose and Throat Disorders	2 (1.3)
Exercise Physiology	6 (3.9)
Eyes and Vision	7 (4.6)
Fertility Regulation	3 (2.0)
Gynecological Cancer	1 (0.7)
HIV/AIDS	2 (1.3)
Heart	11 (7.1)
Hepato-Biliary	4 (2.6)
Immune System	3 (1.9)
Incontinence	1 (0.7)
Infectious Diseases	2 (1.3)
Inflammatory Bowel Disease and Function	2 (1.3)
Lung Cancer	1 (0.7)
Menstrual Disorders and Subfertility	3 (2.0)
Metabolic and Endocrine Disorders	6 (3.9)
Musculoskeletal	8 (5.2)
Neuromuscular Disease	1 (0.7)
Oral Health	3 (2.0)
Other	17 (11.0)
Pain, Palliative and Supportive Care	1 (0.7)
Peripheral Vascular Diseases	4 (2.6)
Pregnancy and Childbirth	5 (3.3)
Prostatic Diseases and Urologic Cancers	1 (0.7)
Public Health	1 (0.7)
Renal	7 (4.6)
Schizophrenia	4 (2.6)
Skin	6 (3.9)
Stroke	4 (2.6)
Tobacco Addiction	1 (0.7)
Upper Gastrointestinal and Pancreatic Diseases	2 (0.7)
Wounds	1 (0.7)

RCT = randomized controlled trial

Outcomes and conclusions (N=154)

Variable	n (%)	Overall risk of bias assessment		
		High	Unclear	Low
Primary outcome				
Objective	74 (48.1)	33	41	0
Subjective	80 (51.9)	39	40	1
Source of outcome assessment				
Administrative data	7 (4.6)	4	3	0
Automated data	21 (13.6)	10	11	0
Clinician assessment	54 (35.1)	24	29	1
Laboratory measure	36 (23.4)	14	22	0
Self-report	36 (23.4)	21	15	0

Risk of bias assessments by domain (N=161)*

Domain	Risk of bias assessments – n (%)		
	High	Unclear	Low
Sequence generation	1 (0.6)	75 (46.6)	85 (52.8)
Allocation concealment	3 (1.9)	124 (77.0)	34 (21.1)
Blinding	21 (13.0)	79 (49.1)	61 (37.9)
Incomplete data	29 (18.0)	30 (18.6)	102 (63.4)
Selective reporting	17 (10.6)	19 (11.8)	125 (77.6)
Other sources of bias	33 (20.5)	90 (55.9)	38 (23.6)
Overall risk of bias	74 (46.0)	86 (53.4)	1 (0.6)

*All studies assessed for risk of bias

Risk of bias assessments by domain (N=154)*

Domain	Risk of bias assessments – n (%)		
	High	Unclear	Low
Sequence generation	0 (0.0)	70 (45.5)	84 (54.6)
Allocation concealment	2 (1.3)	119 (77.3)	33 (21.4)
Blinding	21 (13.6)	75 (48.7)	58 (37.7)
Incomplete data	29 (18.8)	27 (17.5)	98 (63.6)
Selective reporting	16 (10.4)	19 (12.3)	119 (77.3)
Other sources of bias	33 (21.4)	86 (55.8)	35 (22.7)
Overall risk of bias	72 (46.8)	81 (52.6)	1 (0.7)

*Non-intervention studies from original sample replaced with trials evaluating healthcare interventions